

Stereoselectivity in the Reduction of Ketones by Metal Hydrides

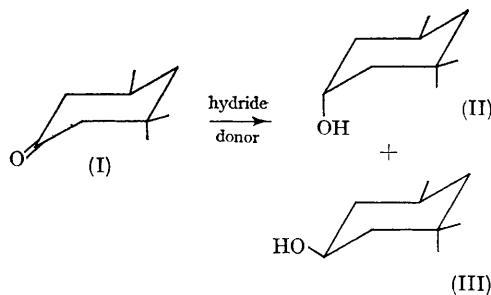
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LITHIUM ALKOXYALUMINOHYDRIDES are often used¹ as selective reducing agents and are normally prepared by addition of the required proportion of an alcohol to lithium aluminium hydride. As an alternative method of obtaining these reagents we have examined the interaction between aluminium alkoxides and lithium aluminium hydride in diethyl ether which affords alkoxyaluminium hydrides by reversal of the equilibrium (IV).

The reduction of benzophenone by lithium aluminium hydride was much slower in the presence of an excess of aluminium isopropoxide (8 equiv.) consistent with modification of the reducing species. Further evidence of hydride ion capture by reversal

of (IV) and of consequent stereoselective reduction was obtained with dihydroisophorone (I):



TABLE

Reduction with lithium aluminium hydride (1—6) and aluminium hydride (8—13) for 2 hours in diethyl ether under nitrogen

	Alkoxide added (8 equiv.)				Temp. °C	% of total alcohol		<i>trans/cis</i> - Ratio
						(II)	(III)	
1	None	(<i>cf.</i> ref. 6)	0	62	38	1.63
2	None	(<i>cf.</i> ref. 2)	34	53	47	1.18
3	Al(OPr ^t) ₃	0	71	29	2.45
4	Al(OPr ^t) ₃	34	55	35	1.57
5	Al(OBu ^t) ₃	0	73	27	2.68
6	Al(OBu ^t) ₃	34	68	32	2.16
7	With LiAl(OBu ^t) ₃ hydride ²	34	70	30	2.33
8	None	0	79	21	3.73
9	None	34	74	26	2.82
10	Al(OPr ^t) ₃	0	69	31	2.23
11	Al(OPr ^t) ₃	34	57	33	1.73
12	Al(OBu ^t) ₃	0	74	26	2.86
13	Al(OBu ^t) ₃	34	68	32	2.15

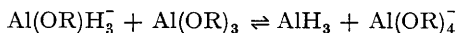
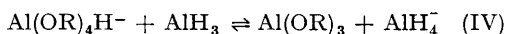
Experiments 4 and 11 have been corrected by deducting the yields from Meerwein-Ponndorf reduction which accounts for 10% of the total reaction. The results were obtained in duplicate by g.l.c. on a Tide column and the *trans/cis*-ratio was calculated before the yields were rounded to whole numbers.

The *trans*-alcohol (II) used as a marker was characterised by its n.m.r. spectrum where the equatorial proton at C-1 absorbs at τ 5.87, $J = 3$ c/sec. The two alcohols were also distinguished on column following partial acylation of the mixture, which increases the *trans/cis*-ratio owing to the greater rate of reaction of the latter³ (III).

Lithium isopropoxyaluminium hydrides are equivalent to lithium aluminium hydride itself under the usual conditions. It has been suggested² that this is due to a rapid disproportionation;



by a sequence culminating in steps of the type (R = Pr^t):

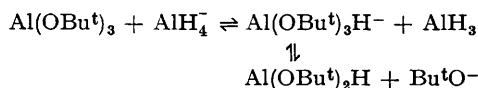


Experiments 3 and 4 show that when isopropoxide is present in excess a different steric result is obtained than with lithium aluminium hydride alone (experiments 1 and 2). This provides indirect support for the disproportionation mechanism since a new reducing species is expected under our conditions by reversal of (IV).

The recovery of unreacted ketone ranged from 30—50% in experiments 3—6 but nevertheless there was no significant equilibration of products as judged by the recovery of a test mixture under the reaction conditions. The small proportion of the more stable *cis*-alcohol obtained in these kinetically controlled reductions could have been formed by approach of the trialkoxyaluminumhydride ion from the more hindered side, or by a competing reduction by aluminium hydride present in the equilibrium (IV), or both. Participation by aluminium hydride was thought possible in view of the reduced

rate of reaction as compared with lithium aluminium hydride alone and because of the report² that 88% of *cis*-alcohol was formed when dihydroisophorone was treated with aluminium hydride. The amount of recovered ketone (40—80%, experiments 10—13) was only slightly higher with aluminium hydride which must therefore compete in the presence of alkoxide. When prepared^{1,2} in ether and used alone with no Lewis acid in excess it produced a greater yield of *trans*-alcohol than the other hydride donors under kinetic control; this should prove a useful general route to axial alcohols. On addition of aluminium chloride (5%) equilibration occurred⁴ under the conditions of experiment 9 affording 88% of *cis*-alcohol as previously reported.

The similarity of product ratios with lithium aluminium hydride and aluminium hydride in the presence of isopropoxide is also evidence of competing reduction. The results obtained (experiments 5 and 12: 6 and 13) with the two reagents and *t*-butoxide at two temperatures are yet closer and the ratios found at 34° compare with that given for lithium tri-*t*-butoxyaluminumhydride. This is evidence of a common reducing agent which may well be di-*t*-butoxyaluminumhydride⁵ derivable from the *t*-butoxide and aluminium hydride by exchange and from lithium aluminium hydride as follows:



In all these reductions a higher yield of the major product was obtained at the lower temperature⁶ and the *trans/cis*-ratio is increased by working below 0°.

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¹ H. C. Brown and Nung Min Yoon, *J. Amer. Chem. Soc.*, 1966, **88**, 1464.

² H. Haubstock and E. L. Eliel, *J. Amer. Chem. Soc.*, 1962, **84**, 2363.

³ E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, 1965, p. 76.

⁴ E. L. Eliel and M. N. Rerick, *J. Amer. Chem. Soc.*, 1960, **82**, 1367.

⁵ H. C. Brown and H. R. Deck, *J. Amer. Chem. Soc.*, 1965, **87**, 5620.

⁶ P. T. Lansbury and R. E. MacLeay, *J. Org. Chem.*, 1963, **28**, 1940.